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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,958	07/16/2003	Steven J. Locke	570002000100	2039

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EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,958	LOCKE ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 29, 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 29* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☒ Claim(s) *1-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' reply filed April 29, 2005, which amended claims 1-10, 12-15, 18, 20-27 and 29. Currently, claims 1-27 and 29 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed May 9, 2005, fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

Claim 6 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 101

Claim 27 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, claims 1-3, 24-27 and 29 have been amended to recite the added limitation "wherein the reagents are directly labeled." The processes of "direct labeling" or "directly labeling", or the physical parameter(s) thereof characterizing the processes of "direct labeling" or "directly labeling" do not appear in the specification, as originally filed, and constitutes new matter.

Claims 1-27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-3, the recitation of "derivatives" is indefinite because it is not clear whether said "derivatives" corresponds to "molecules" recited in the preamble of each claim.

In claims 2-3, 20, 25-26 and 29, the recitations of "the amine" lack antecedent bases. In addition, the recitation of the pronoun "its" is indefinite because it is not clear what noun "its" references.

In claim 25, the second recitation of "comprising" is indefinite because it is not clear what noun is the subject of "comprising."

Claim 27 provides for the use of mass spectrometer, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

Claims 2-6, 8-15, 17-23, 25, 27 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Aebersold et al. (US 6,670,194).

Aebersold et al. teach a method for the quantitative analysis (see Title, "Quantitative Analysis") of a sample of molecules (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell

homogenates; cell fractions; biological fluids..." etc.) having an amine (see col. 10, lines 30-41, "PRGs... include... those that react with amino groups") bearing an active hydrogen comprising the steps of: reacting the molecules with differential isotope labeled reagents (see col. 11, lines 35-39, "the proteins in each sample are reacted with affinity tagging reagents which are substantially chemically identical but differentially isotopically labeled") resulting in the reductive alkylation of the amines (see col. 10, lines 50-52, "amino reactive groups include aldehydes... in the presence... of $NaBH_4$ or $NaCNBH_4$") to their alkylamine derivatives, such that the alkylamine derivatives are isotopically labeled (see Abstract, "The linker may be differentially isotopically labeled"), and examining the derivative by mass spectrometry (see Abstract, "reaction products are characterized by mass spectrometric (MS) techniques"). Examiner posits that Aebersold et al. explicitly teach a reaction of aldehydes (belonging to the PRGs) and amino groups (belonging to sample proteins) in the presence of $NaBH_4$ or $NaCNBH_4$. Consequently, the claimed "amine bearing an active hydrogen" and "alkylamine derivatives" necessarily result from this teaching of Aebersold et al. and would be so recognized by persons of ordinary skill in the art.

With respect to claims 3 and 29, Aebersold et al. teach a method for the quantitative analysis of two or more samples (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell homogenates; cell fractions; biological fluids..." etc.). In addition, Aebersold et al. teach the step of combining the derivatized molecules (see col. 6, lines 2-3, "The treated samples are then combined").

With respect to claims 4 and 29, Aebersold et al. teach a method comprising an additional step of cleaving the derivatized molecules prior to examining by mass spectrometry (see col. 6, lines 3-4).

With respect to claim 5, Aebersold et al. teach a method comprising an additional step of denaturing the molecules prior to reacting with isotopically labeled reagents (see col. 12, line 4-6).

With respect to claim 6, Aebersold et al. teach a method wherein electrospray ionization is used (see col. 11, lines 58-59).

With respect to claims 8-9, 11 and 29, Aebersold et al. teach a method comprising an additional step of separating derivatized molecules by 1D gel electrophoresis, 2D gel electrophoresis, or HPLC before examining by mass spectrometry (see col. 36, lines 11-12).

With respect to claim 10, Aebersold et al. teach a method comprising an additional step of separating the fragments after cleaving (see col. 19, lines 41-43).

With respect to claims 12-14 and 29, Aebersold et al. teach a method comprising an additional step of analyzing the preparation by CID in MS/MS mode to sequence the molecule (see col. 36, lines 19-36).

With respect to claims 15 and 17, Aebersold et al. teach a method wherein the isotopically labeled reagents are an aldehyde and a sodium borohydride reducing agent (see col. 10, lines 50-52).

With respect to claims 18-19 and 29, Aebersold et al. teach a method wherein the sample proteins are extracted from cells (see col. 5, line 63, "cell or tissue lysates").

With respect to claim 20, Aebersold et al. teach a method wherein the amines are lysine residues and N-terminal amino groups (see col. 18, lines 11-12).

With respect to claims 21-23, Aebersold et al. teach a method wherein an electrospray ionization ion trap spectrometer is used (see col. 22, lines 29-30).

With respect to claim 25, Aebersold et al. describe a preparation comprising a sample (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell homogenates; cell fractions; biological fluids..." etc.) having an amine (see col. 10, lines 30-41, "PRGs... include... those that react with amino groups") bearing an active hydrogen, comprising isotopically labeled derivatives (see Abstract, "The linker may be

differentially isotopically labeled") resulting from the reductive alkylation of the amines (see col. 10, lines 50-52, "amino reactive groups include aldehydes... in the presence... of $NaBH_4$ or $NaCNBH_4$") to their alkylamine derivatives. The claimed "alkylamine derivatives" necessarily results from the aforementioned teaching of Aebersold et al. and would be so recognized by persons of ordinary skill in the art.

With respect to claim 27, Aebersold et al. describe a method comprising a mass spectrometer (see Abstract).

Claim Rejections - 35 USC § 103

Claims 1, 4-15, 17-24 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (US 6,670,194) in view of Figeys et al. (US 2002/0076817).

Aebersold et al. teach a method for the simultaneous (see col. 11, line 40, "The samples are combined and processed as one") quantitative analysis (see Title, "Quantitative Analysis") of at least three samples (see col. 11, lines 35-39, "two or more protein samples", lines 47-54, "cell homogenates; cell fractions; biological fluids..." etc.) comprising the steps of: reacting each sample with differential isotope labeled reagents (see col. 11, lines 35-39, "the proteins in each sample are reacted with affinity tagging reagents which are substantially chemically identical but differentially isotopically labeled") wherein the reagents are directly labeled (see col. 11, lines 35-39, "affinity tagging reagents are... differentially isotopically labeled"), combining the derivatives (see col. 6, lines 2-3, "The treated samples are then combined"), and examining the derivatives by mass spectrometry (see Abstract, "reaction products are characterized by mass spectrometric (MS) techniques").

Aebersold et al. do not teach the step of "reacting the molecules of each sample with at least two differential isotope labeled reagents."

However, Figeys et al. teach the step of reacting each sample with two differential isotope labeled reagents (see Fig. 6, "O^{16}-water" and "O^{18}-water") (see Fig. 6, "Peptides mixture") in order to label individual samples with distinct isotope ratios (see para. [0010]). Therefore, it would have been obvious for a person of ordinary skill in the art to modify the simultaneous quantitative method of Aebersold et al. with the use of two isotopically labeled reagents because Figeys et al. teach that labeling individual samples with distinct isotope ratios allows a convenient means for "sample tracking" which allows a peptide to be traced back to its sample source (see para. [0036]).

With respect to claim 4-6, 8-15, 17-23 and 27, see supra.

With respect to claim 7, Figeys et al. teach a method wherein ionspray is used (see para. [0055]).

With respect to claims 24 and 26, Figeys et al. teach the step of reacting each sample with two differential isotope labeled reagents (see Fig. 6, "O^{16}-water" and "O^{18}-water") (see Fig. 6, "Peptides mixture").

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (US 6,670,194) and Figeys et al. (US 2002/0076817) as applied to claims 1 and 15, and further in view of Vandekerckhove & Gevaert (US 2004/0005633).

Aebersold et al. and Figeys et al. teach a method for the simultaneous quantitative analysis of at least three samples as substantially described supra. The aforementioned references do not teach a method wherein formaldehyde and acetaldehyde are used.

However, Vandekerckhove & Gevaert teach the use of deuterated formaldehyde and acetaldehyde (see para. [0107]) in order to induce a distinguishable mass shift in peptide analysis. Therefore, it would have been obvious for a person of ordinary skill in the art to modify the method of Aebersold et al. and Figeys et al. with the use of formaldehyde and acetaldehyde because Vandekerckhove & Gevaert teach that induction of distinguishable mass shifts, e.g. with deuterated formaldehyde or acetaldehyde, allows isolation and identification of peptides in complex mixtures (see para. [0002] to [0004]).

Response to Arguments

In prior Office Action, claim 27 was rejected under 35 USC §§ 101 and 112, second paragraph, for the recited "use of a mass spectrometer." In response, Applicants have amended claim 27 to recite the use "according to the steps recited in any one of claims 1, 2 or 3". Applicants' amendment is insufficient to overcome these rejections. The term "use" is a legal term of art having several definitions, none of which are disclosed in Applicants' specification or applied to Applicants' invention. The meaning of the term "use" in the context of Applicants' invention is not clear.

In prior Office Action, claims 1-27 and 29 were rejected under various combinations of teachings of Aebersold et al. (US 6,670,194), Figeys et al. (US 2002/0076817) and Vandekerckhove & Gevaert (US 2004/0005633).

In response, Applicants attempt to distinguish their claimed invention from that of Aebersold et al. by alleging that Applicants' invention "does not employ an affinity label and a linker group" (see Applicants' remarks, p. 12, fifth paragraph, "the method of the present invention is a simple, one-step reaction which does not employ an affinity label and a linker group"; p. 13, first full paragraph, "the present invention

does not employ a separate affinity group (A)"). Applicants' argument has been carefully considered but is not persuasive because such a negative claim limitation, i.e. an invention that "does not employ an affinity label and a linker group," is not recited anywhere in Applicants' claims.

In addition, Applicants attempt to distinguish their claimed invention from that of Aebersold et al. by alleging that Applicants' invention is "a one component system" (see Applicants' remarks, p. 12, sixth paragraph, "there is only a one component system employed in the instant invention") involving a "one step reaction" (see Applicants' remarks, p. 14, third full paragraph, "the currently claimed invention of a simple, one-step reaction"). Applicants' argument has been carefully considered but is not persuasive because the phrase "one component system" is indefinite and does not appear to have antecedent support in Applicants' specification. The phrase "one step reaction" is also indefinite. Nevertheless, Aebersold et al. appears to describe a "one step reaction" (see col. 11, lines 35-39, "the proteins in each sample are reacted with affinity tagging reagents which are substantially chemically identical but differentially isotopically labeled").

Finally, Applicants successfully distinguish their claimed invention from that of Aebersold et al. and Figeys et al. by observing that Applicants' claimed invention recites a chemical genus (see Applicants' remarks, p. 14, last paragraph, "the methods of the present invention teach the use of two chemically distinct compounds") (emphasis added), whereas Figeys et al. recite an isotope species (see Applicants' remarks, p. 14, last paragraph, "Figeys et al. describe the use of different proportions of two isotopically distinct components") (emphasis mine) (internal emphasis omitted). Applicants' observation is accurate. See MPEP 2131.02.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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